Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 43-45, 94-126 and 135-182 and 183-200 are pending in the application, with claims 43, 94, 95, 103, 111, 119, 135, 143, 151, 159, 167, 175, 183, 189 and 195 being the independent claims. Claims 127-134 are cancelled without prejudice to or disclaimer of the subject matter therein and represented as claims 183-200 without multiple dependency. Support for new claims 183-200 can be found, *inter alia*, at page 36, lines 10-13 and page 46, lines 1-2. These changes are believed to introduce no new matter, and their entry is respectfully requested. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112

The Examiner rejected claims 127-134 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Specifically, the Examiner alleged that claims directed to polypeptides having at least 90-97% identity to amino acids 69 to 208 of SEQ ID NO:2 are not enabled. Applicants have cancelled claims 127-134 and have added claims 183-200. Applicants respectfully traverse this rejection as it may apply to the pending claims.

In order for a claim to be enabled, the specification must teach one of ordinary skill in the art to make and use the invention without undue experimentation. The factors that can be considered in determining whether an amount of experimentation is undue have been set forth in *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification,

the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *See id.*

In re Wands involved an appeal from the Board of Appeals and Patent Interferences, affirming the examiner, rejecting immunoassay claims on the grounds that making anti-HBsAg antibodies for use in the claimed immunoassay, other than the deposited antibody, would be "unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies." *Id.* at 735, 8 U.S.P.Q.2d at 1402. Antibodies other than the one deposited were described only in terms of function and only a general method of making and using them was disclosed in the application. *See id.* The facts showed that IgM antibodies were disfavored because they tended to self-aggregate and precipitate, isolating the correct antibodies required screening hundreds of clones, and the appellant's first four attempts were unsuccessful. *See id.* at 734, 8 U.S.P.Q.2d at 1402. Nevertheless, the Federal Circuit found that the disclosure satisfied the requirements under 112 first paragraph. The court based its decision on the fact that the invention could be practiced with "readily available starting materials using methods that are well known in the monoclonal antibody art" and because "practitioners of the art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *See id.* at 736, 8 U.S.P.Q.2d at 1406.

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, in *In re Angstadt*, the Court of Custom and Patent Appeals

has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue:

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

537 F.2d at 503, 190 U.S.P.Q. at 219 (emphasis in the original). As Judge Rich explained in *In re Vaeck*, 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility." Applicants submit that, in the instant case, since, as discussed herein, the disclosed or otherwise known methods of making and screening polypeptides which are at least 90% identical to amino acids 69 to 208 of SEQ ID NO:2 may be used to make and then *determine*, without undue experimentation, whether a given polypeptide encompassed by the claims generates specific antibodies, and therefore possesses a disclosed utility, the enablement requirement is fully satisfied. *In re Wands*, 858 F. 2d 731, 8 U.S.P.Q. 2d at 1404; *Ex parte Mark*, 12 U.S.P.Q. 2d 1904, 1906-1907 (B.P.A.I. 1989).

The Examiner relied on *Amgen vs. Chugai*, 927 F.2d 1200, 18 U.S.P.Q. 2d 1016 (Fed. Cir. 1991) in making this rejection. The Examiner quoted *Amgen* and further stated that

> [t]he fact pattern is directly analogous [to *Amgen*] in that what is claimed are polypeptides that have yet to be isolated

> or characterized for the activity recited in the application and thereby constitutes a "wish to know" rather than a reduction to practice, absent evidence to the contrary.

Paper No. 12, page 7.

The passage that the Examiner quoted from *Amgen* does not relate to enablement. Rather, the passage deals with whether or not particular claims were invalid under 35 U.S.C. § 102(g). In *Amgen*, one of the claims was directed to an isolated and purified gene encoding human EPO. The 102(g) issue was whether the knowledge of the existence of a gene and a method for isolating it is adequate conception to constitute a prior invention under 35 U.S.C. § 102(g). The alleged prior inventor had knowledge of the existence of the EPO gene, as well as a plan for cloning the gene, but did not actually know the sequence of the gene. The court held that in order for an inventor of an isolated and purified gene to have priority, the inventor must have actually isolated the gene or know its sequence. In the present case, the issue is not whether the inventors actually reduced the invention to practice, but whether the disclosure enables one of ordinary skill in the art to practice the claimed invention.

Nevertheless, the inventors have actually sequenced the gene for KGF-2, and have constructed at least one truncated form of the gene and polypeptide, KGF-2Δ33. In addition, the amino acid sequence of all of the polypeptides of the claims are known and can readily be made, based on the sequence identity with the truncated form of KGF-2 recited in the claims.

Applicants point out that in order to enable the claimed invention as required by 35 U.S.C. § 112, first paragraph, the specification need only enable a person of ordinary skill in the art to make the claimed polypeptides and practice a single use of the claimed

polypeptides without undue experimentation.[1] Thus, Applicants submit that to be fully enabled, the claimed polypeptides need merely have application in a single use, such as, for example, to raise antibodies to the native protein.

The Examiner stated that "[i]n order to use the claimed invention, the polypeptides which are claimed would need to retain the activity (immunogenic or biological) of the polypeptide which has the amino acid sequence of SEQ ID NO:2 in order for one of ordinary skill to use what is claimed. . . The specification provides no guidance as to which amino acids (i.e. structural elements) of the native proteins are critical to the biological/immunological activity or which amino acids could be altered without destroying these activities." Paper No. 12, page 6.

Contrary to the Examiner's assertion, the specification does provide, at page 32, lines 19-27, and at page 40, lines 7-16, the antigenic regions of KGF-2. Five of these antigenic regions fall completely within amino acids 69 to 208 of SEQ ID NO:2. The Examiner states that the "claims encompass polypeptides which differ from the native polypeptide by the substitution, insertion, deletion or modification of as many as 14 amino acids." Paper No. 12, page 9. Assuming this is true, one of ordinary skill in the art, using the guidance provided in the specification, would know not to alter at least one of the antigenic regions disclosed in the specification in order to obtain a polypeptide useful for raising antibodies.

Further, even though only one use needs to be enabled, Applicants have provided, at Figure 2, an alignment of KGF-2 with other fibroblast growth factors. One of ordinary

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[1] The Applicant need show utility for only one disclosed purpose. See *Raytheon Co. v. Roper Corp.*, 724 F. 2d 951, 220 U.S.P.Q. 592 (Fed. Cir. 1983, *cert. denied*, 469 U.S. 835 (1984); *Ex parte Lanham*, 121 U.S.P.Q. 223 (Pat. Off. Bd. App. 1958).

skill in the art would know not to alter the residues which are conserved across these molecules in order to obtain a KGF-2 variant with biological activity.

In addition, the specification discloses, for example, on page 45, several polypeptides falling within the scope of the claims. The specification also provides guidance, on page 51, for particular amino acid substitutions which may be made in the amino acids 69 to 208 of SEQ ID NO:2. Numerous examples of KGF-2Δ33 polypeptides with amino acid substitutions are provided in Example 22, at page 152 to page 160. Further, the specification demonstrates that a polypeptide consisting of amino acids 63 to 208 of SEQ ID NO:2 (also known as KGF-2Δ28), which falls within the scope of the claims, is biologically active. *See*, for example, page 121, lines 6-8; page 127, lines 20-24. Thus, the specification provides ample direction for one of ordinary skill to make and use the polypeptides of the invention.

As of the filing date of the instant application, there was a high level of skill in the field of protein chemistry and molecular biology. Techniques were available for routinely making polypeptides and generating antibodies that bind these polypeptides. The Examiner has not considered the fact that the invention could be practiced with readily available starting materials using methods that were well known in the art on the priority date of the instant application. Like the monoclonal antibody art discussed in *In re Wands*, practitioners making the polypeptides of the invention are prepared to screen for antibody binding activity.

Applicants assert that the Examiner has underestimated the level of skill of the skilled artisan. Applicants submit that the skilled protein chemist or molecular biologist,

enlightened by the teaching of the present specification, is more than capable of routinely determining whether a polypeptide encompassed by the claims binds a specific antibody.

Further, it was known in the art that, as a general matter, proteins are functionally resilient to modification. *See, e.g.*, Bowie, J.U. *et al.* "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science* 247:1206-1210 (1990). Bowie *et al.* teach that the "message [for encoding proteins] is highly degenerate in that many different sequences can code for proteins with essentially the same structure and activity"; and that "proteins are surprisingly tolerant of amino acid substitutions." *Id.* at 1206. An exemplary protein supporting this proposition is the beta subunit of hemoglobin. It is well-known in the art that the majority of amino acid substitutions within the beta subunit of hemoglobin are functionally "silent." *See, e.g.,* Hutt *et al. Hemoglobin* 20(4):371-6 (1996) ("Approximately 700 hemoglobin variants have been reported, causing a variety of clinical manifestations, with the majority being clinically silent."). *See also* Arous *et al., FEBS Lett.* 147 (2):247-50 (1982); Ramachandran *et al.*, *Hemoglobin* 16(4):259-66 (1992). Thus, contrary to the suggestion made by the Examiner, Applicants assert that, in general, proteins are resilient to modification and retain functional activity notwithstanding numerous amino acid substitutions, deletions and/or insertions.

In view of the resiliency of proteins to modification and given the fact that structurally and functionally significant regions of KGF-2 have been disclosed in the specification, it would not require undue experimentation for one of ordinary skill in the art to make polypeptides which are at least 90-97% identical to the amino acids 69 to 208 of SEQ ID NO:2 and determine which polypeptides have the utility of generating KGF-2 binding antibodies. Experimentation is not undue merely because it would require

assaying multitudes of variants encompassed by the claimed invention. As set forth in *In re Wands*, "[t]he test is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine." 858 F.2d at 737, 8 U.S.P.Q.2d at 1404. The Examiner is reminded again that in *In re Wands*, the Applicant had to screen hundreds of clones to find one that met the limitations of the claims. *See id.* at 736, 8 U.S.P.Q.2d at 1406.

Applicants specifically point out that assaying polypeptides for ability to bind a specific antibody would be routine because assays for antibody binding were routine in the art at the time the invention was made. The Examiner has provided no objective evidence showing that making the polypeptides of the claims and assaying for antibody binding activity were not routine to one of skill in the art at the time the invention was made.

Applicants submit that because of: (1) the availability of routine techniques for synthesizing peptides; (2) the knowledge of the amino acid sequence constituting KGF-2; (3) the overall functional resiliency of proteins to changes in their amino acid sequence ; (4) the availability of routine techniques for generating antibodies; (5) the high level of skill in the field of protein chemistry and molecular biology; and (6) the direction and guidance provided by the specification regarding KGF-2 polypeptides, one skilled in the art could routinely make and use the polypeptides of the invention. Accordingly, withdrawal of this rejection is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the

Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Andrea Jo Kamage

Andrea Jo Kamage
Agent for Applicants
Registration No. 43,703

Date: 3/14/02

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600
P108-64.wpd

Version with markings to show changes made

Claims 127-134 have been cancelled.

The following new claims have been added.

183. (new) An isolated polypeptide comprising an amino acid sequence at least 90% identical to Ser (69) - Ser (208) of SEQ ID NO:2.

184. (new) The isolated polypeptide of claim 183, having a Met residue at the N-terminus of said amino acid sequence.

185. (new) The isolated polypeptide of claim 183, wherein said polypeptide is part of a fusion protein.

186. (new) The isolated polypeptide of claim 183, which is produced in a recombinant cell.

187. (new) The isolated polypeptide of claim 186, wherein said recombinant cell is bacterial.

188. (new) The isolated polypeptide of claim 183, together with a pharmaceutically acceptable carrier or excipient.

189. (new) An isolated polypeptide comprising an amino acid sequence at least 95% identical to Ser (69) - Ser (208) of SEQ ID NO:2.

190. (new) The isolated polypeptide of claim 189, having a Met residue at the N-terminus of said amino acid sequence.

191. (new) The isolated polypeptide of claim 189, wherein said polypeptide is part of a fusion protein.

192. (new) The isolated polypeptide of claim 189, which is produced in a recombinant cell.

193. (new) The isolated polypeptide of claim 192, wherein said recombinant cell is bacterial.

194. (new) The isolated polypeptide of claim 189, together with a pharmaceutically acceptable carrier or excipient.

195. (new) An isolated polypeptide comprising an amino acid sequence at least 97% identical to Ser (69) - Ser (208) of SEQ ID NO:2.

196. (new) The isolated polypeptide of claim 195, having a Met residue at the N-terminus of said amino acid sequence.

197. (new) The isolated polypeptide of claim 195, wherein said polypeptide is part of a fusion protein.

198. (new) The isolated polypeptide of claim 195, which is produced in a recombinant cell.

199. (new) The isolated polypeptide of claim 198, wherein said recombinant cell is bacterial.

200. (new) The isolated polypeptide of claim 195, together with a pharmaceutically acceptable carrier or excipient.